

### **Remarks/Arguments**

By the present amendment, applicants have amended Claims 35, 50, and 52. The claims remaining for consideration by the Examiner are Claims 35-54.

The Examiner has rejected Claims 35-54 under 35 U.S.C. 112, first paragraph, for failing to comply with the written description requirement. The Examiner states that there is no literal support in the specification for the term "multidosage".

In response, applicants have amended Claims 35, 50, and 52 to remove the term "multidosage". However, applicants direct the Examiner's attention to page 11, lines 29-31, of applicants' specification wherein applicants state that the invention provides a cartridge containing a single dose or multiplicity of doses of a liquid human growth hormone formulation according to the invention.

The Examiner has rejected Claims 35-51 under 35 U.S.C. 102(b) as being anticipated by WO 94/03198 ('198).

To be anticipated by a reference, the claimed invention must be identically disclosed in the reference. WO '198 describes suitable pH ranges for human growth hormone formulations from about 4 to about 8, more preferably about 5.5 to about 7, most advantageously 6.0. The formulations in the examples of WO '198 have a pH of 6.0.

In contrast, applicants' hGH formulations, as claimed, have a pH range of 6.15 to 6.5. WO '198 does not teach a pH range of 6.15 to 6.5 for the hGH formulations. Thus, WO '198 fails under 35 U.S.C. 102(b) to anticipate applicants' invention, as claimed.

The Examiner has rejected Claims 35-44, 48, 50, and 51 under 35 U.S.C. 102(b) as being anticipated by U.S. Patent No. 5,096,885 ('885).

The '885 patent describes suitable pH ranges for human growth hormone formulations from about 4 to about 8, advantageously about 6 to about 8, most advantageously 7.4.

In contrast, applicants' hGH formulations, as claimed, have a pH range of 6.15 to 6.5. The '885 patent does not teach a pH range of 6.15 to 6.5 for the hGH formulations. Thus, the '885 patent fails under 35 U.S.C. 102(b) to anticipate applicants' invention, as claimed.

The Examiner has rejected Claims 52-54 under 35 U.S.C. 103(a) as being unpatentable over WO'198 in view of U.S. Patent No. 5,334,162 ('162).

In Example I of WO '198, the chemical stability of aqueous hGH formulations was analyzed by anion exchange HPLC. Formulation samples were stored at 2-8°C for 18 months, and 40°C for at least 28 days, to study the amount of deamidated hGH. As stated on page 10, lines 25-27, WO '198 determined that "[a]lthough the rate of deamidation is faster in the aqueous state (as compared to lyophilized hGH), this rate is minimized at pH 6.0 and below". Thus, according to the teachings of WO '198, the degradation of hGH in aqueous formulations is minimized at pH 6.0 and below.

In contrast to the teachings of WO '198, applicants determined that crystallization of hGH is minimized as determined by the absence of crystal formation in liquid hGH formulations at a pH from 6.15 to 6.5, as claimed.

The basis for applicants' pH range determination is found in applicants' specification in Example 4. In Example 4, applicants evaluated the stability of aqueous hGH formulations. A series of pH variants in 0.1 increments were made by adjusting the respective amounts of phosphate buffer in applicants' Formulation VI. The formulations were stored at 15°C for up to 3 months, and the presence or absence of crystals was observed during the storage period. As stated in Example 4, crystallization was observed in formulations below pH 6.2, i.e., at pH 6.1, and no crystallization was observed in formulations having a pH of 6.2 and above.

In Example 4, applicants also evaluated the stability of an aqueous hGH formulation, Formulation V, having a pH of 6.0. As stated in Example 4, Formulation V exhibited crystallization when stored at 15°C and 25°C within 6 weeks, and crystallization when stored at 2-8°C within 2-3 months. Thus, applicants determined that the stability of aqueous hGH formulations is significantly affected by the pH of the formulation.

While WO '198 describes suitable pH ranges from about 4 to about 8, WO '198 clearly states that the formation of degradation products are minimized during storage at a pH of 6.0 or below. It is impermissible within the framework of 35 U.S.C. 103 for the Examiner to pick and choose from a reference only so much of it as will support a given position to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one skilled in the art. *Bausch @ Lomb, Inc. v. Barnes-Hindl Hydrocurve, Inc.*, 230 U.S.P.Q. 416 (Fed. Cir. 1986). WO '198 teaches that the chemical stability of aqueous hGH formulations is deleteriously effected by a pH greater than 6.0. Thus, one skilled in the art studying the teachings of WO '198 and attempting to formulate storage stable liquid hGH formulations, as claimed by applicants, would not be expected to choose a pH greater than 6.0.

Applicants' claims are limited to liquid hGH formulations having a pH of 6.15 to 6.5. WO '198 tries to avoid a pH above 6.0 because of the formation of deamidated hGH during storage. This is the very antithesis of obviousness.

With regard to the '162 patent, this patent describes a cartridge assembly for holding a lyophilized drug. As stated in applicants' specification, on page 2, lines 3-5, lyophilized products need reconstitution immediately or shortly prior to administration. Reconstitution of the lyophilized drug in the '162 patent is accomplished by the use of an obliquely angled connector which causes a diluent to indirectly impinge on the drug. The '162 patent mentions hGH as an example of a lyophilized compound, however, the '162 patent does not teach or suggest any hGH formulations or any drug formulations. In addition, the '162 patent does not teach or suggest pH.

Assuming, for the sake of argument, that WO'198 and the '162 patent may be properly combined, as suggested by the Examiner, one skilled in the art would not be in possession of applicant's invention, as claimed. There is no teaching or suggestion in either reference to prepare a storage stable hGH formulation having a pH of 6.15 to 6.5. In fact, as noted above, WO'198 teaches away from using a pH above 6.0 because of the formation of deamidated hGH during storage.

The Examiner has rejected Claims 45-47 under 35 U.S.C. 103(a) as being unpatentable over '885.

The '885 patent is based on the discovery that the use of glycine and mannitol as the lyophilizing bulking matrix in a hGH formulation inhibits dimer formation during storage. Glycine is an amino acid which according the '885 patent "greatly inhibits dimer formation" when added in a molar ratio hGH:glycine of 1:50-200, as stated in column 5, lines 29-32.

In contrast, applicants claim a storage stable liquid human growth hormone formulation consisting essentially of growth hormone in isotonic phosphate buffered solution, a preservative and a non-ionic surfactant, wherein isotonicity of the phosphate buffered solution is provided by a compound selected from the group consisting of a neutral salt, a monosaccharide, a disaccharide, and a sugar alcohol. The language "consisting essentially of" renders applicants' claims open only to the inclusion of ingredients that do not materially affect the basic and novel characteristics of the claimed formulation. It is clear from applicants' claim language and specification that glycine is not included in any of the claimed elements. Thus, the '885 patent does not render applicants' claims obvious.

In column 5, lines 16-19, the '885 patent states that suitable pH ranges for the formulations are from about 4 to about 8, advantageously about 6 to about 8, most advantageously 7.4. However, in column 5, lines 19-22, the '885 patent states that the pH should be less than 7.5 to reduce deamidation, and pH values below 7.0 result in particulate formation upon lyophilization.

In contrast to the teachings of the '885 patent, applicants unexpectedly determined that the crystallization of hGH is minimized as determined by the absence of crystal formation in liquid hGH formulations at a pH from 6.15 to 6.5, as claimed.

While the '885 patent describes suitable pH ranges from about 4 to about 8, the '885 patent clearly states that pH values below 7.0 result in particulate formation. Thus, one skilled in the art studying the teachings of the '885 patent and attempting to formulate storage stable hGH formulations, as claimed by applicants, would not be expected to choose a pH less than 7.0. The '885 patent, therefore, does not render applicants' claims obvious.

The Examiner has rejected Claims 52-54 under 35 U.S.C. 103(a) as being unpatentable over U.S. '885 in view of '162.

As discussed above, the '885 patent states that pH values below 7.0 result in particulate formation. Thus, one attempting to formulate stable hGH formulations which can be stored at home in a domestic refrigerator for at least a few months without aggregation occurring, as stated in applicants' objectives in the specification, on page 4, lines 2-8, would not be motivated to use a pH less than 7.0. The '885 patent, therefore, teaches away from applicants' claimed pH range of 6.15 to 6.5.

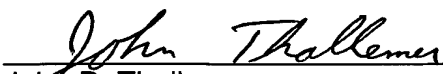
As discussed above, the '162 patent describes a cartridge assembly for holding a lyophilized drug. The '162 patent mentions hGH as an example of a lyophilized compound, however, the '162 patent does not teach or suggest any hGH formulations or any drug formulations. In addition, the '162 patent does not teach or suggest pH.

Assuming, for the sake of argument, that the '885 patent and the '162 patent may be properly combined, as suggested by the Examiner, one skilled in the art would not be in possession of applicant's invention, as claimed. There is no teaching or suggestion in either reference to prepare a storage stable hGH formulation having a pH of 6.15 to 6.5. In fact, as noted above, the '885 patent teaches away from using a pH less than 7.0 where particulate formation may be a problem, such as during storage over a period of months.

In view of the above amendments and arguments, it should be unambiguously clear that none of references cited by the Examiner evaluated alone or in combination suggest applicants' hGH formulation, as claimed.

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